Journal of NeuroVirology, 14: 474–479, 2008

ISSN 1355-0284 print / 1538-2443 online
DOI: 10.1080/13550280802195367

informa
healthcare

Acute meningoencephalitis due to human immunodeficiency virus type 1 infection in 13 patients: clinical description and follow-up

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The objective of this study is to describe a series of cases of severe meningitis caused by human immunodeficiency virus type 1 (HIV-1) occurring during primary infection or after antiretroviral treatment interruption. In an observational cohort study, 13 patients with clinical diagnosis of meningitis or meningoencephalitis were reviewed. Ten cases occurred during primary HIV-1 infection and 3 after antiretroviral therapy (ART) withdrawal. Demographic parameters, clinical presentation and outcome, and laboratory and cerebrospinal fluid (CSF) parameters were recorded. The risk factor for HIV-1 infection acquisition was sexual transmission in all cases. The most frequent systemic symptoms were fever (12/13) and headeache (9/13). Among neurologic symptoms, focal signs appeared in seven patients (53.8%), confusion in six (46.2%), and agitation in five (38.5%). The median CD4 cell count was 434 cells/mm3. In all cases, CSF was a clear lymphocytaire fluid with normal glucose levels. Cranial computerized tomography was performed in seven patients, with a normal result in all of them; brain magnetic resonance in eight patients was normal in five cases and showing cortical atrophy, limbic encephalitis, and leptomeningeal enhancement in one patient each. The electroencephalographs (EEG) just showed diffuse dysfunction in three cases. ART was started in 11 patients. HIV RNA load at 12 months was <50 copies/ml in all treated patients. The 13 patients recovered without neurologic sequela. Meningitis or meningoencephalitis during primary HIV-1 infection or after ART cessation are unusual but sometimes a life-threatening manifestation. Although all patients tend to recover and the necessity of ART is not well established, some data suggest its potential benefit in these patients. *Journal of NeuroVirology* (2008) **14,** 474–479.

Keywords: Primary HIV infection; acute retroviral syndrome; central nervous system involvement; meningitis; meningoencephalitis; antiretroviral therapy; HIV-1

Introduction

It is estimated that 40% to 90% of patients with primary human immunodeficiency virus type 1 (HIV-1) infection experience an acute retroviral syndrome; however, the nonspecific nature of the acute symptoms in most cases results in under diagnosis of this entity (Bachmeyer *et al,* 1997; Li *et al,* 2002; Atwood *et al,* 1993; Schacker *et al,* 1996, 1998). Although neurological presentations, including aseptic meningitis, have been described in 17% to 24% of these patients, severe cases of meningitis

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This work was partially supported by the Red Temática Cooperativa de Grupos de Investigación en Sida del Fondo de Investigación Sanitaria (FIS), and grants from ISCIII-RETIC RD06/006 and FIS 04-0363, Instituto de Salud Carlos III, Madrid, Spain. Dr. J. M. Miró received a research grant from the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and the Conselleria de Salut de la Generalitat de Catalunya, Barcelona, Spain.

Received 3 March 2008; revised 18 March 2008; accepted 16 April 2008.

have been rarely reported (Schacker *et al,* 1998; Newton *et al,* 2002). Some authors suggest that patients who present neurological features during primary HIV infection may experience faster progression of HIV-related disease (Boufassa *et al,* 1995; Wallace *et al,* 2001).

An acute retroviral syndrome similar to what occurs during primary HIV infection has also been described during treatment interruptions (Colven *et al,* 2000), and cases of acute meningitis have been reported in this setting (Worthington and Ross, 2003; Breton *et al,* 2003).

In this study, a case series is presented of patients with severe HIV-1 meningitis occurring during the primary infection or after interruption of antiretroviral treatment. The clinical presentation of these patients and their evolution after recovery are described.

Results

Acute meningitis or meningoencephalitis was diagnosed in 13 patients, 10 during primary HIV infection and 3 in chronic HIV-infected patients after antiretroviral treatment interruption.

There were seven (53.8%) women and six (46.2%) men, with a median age of 39 (IQR: 32–54) years. HIV infection was acquired by sexual transmission in all cases (men who had sex with men in six cases and heterosexual in seven). The patients' clinical manifestations are summarized in Table 1. Among the neurological symptoms, a focal neurological sign was present in 53.8% of the cases, the most striking of these being ataxia, dysarthria, unilateral Bell palsy, and paresthesia. One patient also presented with uveomeningitis. Nearly half the patients had confusion or obtundation (46.2%). In contrast, only two patients had meningeal signs.

Table 1 Clinical manifestations in patients with meningitis due to HIV-1 infection

	PHI[a]	CHI[b]	Total[c]
No. of cases	10	3	13
Systemic symptoms			
Fever	10	2	12 (92.3)
Headache	8	1	9 (69.2)
Gastrointestinal symptoms	7	1	8 (61.5)
Lymph adenopathy	5	2	7 (53.8)
Sore throat	7	0	7 (53.8)
Rash	6	0	6 (46.2)
Neurological symptoms			
Focal neurological signs	5	2	7 (53.8)
Confusion/obtundation	5	1	6 (46.2)
Agitation	4	1	5 (38.5)
Seizures	2	0	2 (15.4)
Meningeal signs	1	1	2 (15.4)

[a]PHI = primary HIV infection.
[b]CHI = chronic HIV infection. Cases after antiretroviral therapy withdrawal.
[c]No. (%).

Table 2 shows the laboratory findings in blood and CSF of all patients. Median CD4 lymphocyte count was 434 (IQR: 289.5–577.5) cells/mm^3. Plasma HIV RNA ranged from 5100 (3.71 $\log_{10}$) to 22,000,000 (7.34 $\log_{10}$) copies/ml. In all cases, CSF was a clear fluid with normal glucose levels and a predominance of lymphocytes. ADA levels determined in 10 patients yielded a median of 7.5 (IQR: 4.75–10.25). In two patients, ADA levels were >10 IU/L.

In 7 of the 13 cases, we also recorded CSF HIV RNA load. In five patients with meningitis during primary infection, mean HIV viral load in CSF was 5.6 $\log_{10}$, as compared to 4.1 $\log_{10}$ in those who presented neurological symptoms after withdrawal of antiretroviral therapy.

Cranial computerized tomography was performed in seven patients, with normal results in all of them. Brain magnetic resonance was performed in eight cases, with the following findings: normal in five cases, cortical atrophy, limbic encephalitis and leptomeningeal enhancement in one patient each. EEG was performed in four patients, and diffuse dysfunction was observed in three of them.

All patients recovered from meningitis without neurological sequelae. The median hospital stay was 12 (range 6–22) days, and all patients were completely recovered at discharge. On the diagnosis of HIV meningitis or meningoencephalitis, antiretroviral therapy was started in 11 of the 13 patients. The different antiretroviral regimens and the CNS Penetration-Effectiveness Score for each patient are shown in Table 3. Plasma HIV RNA viral load at 12 months was <50 copies/ml in all the treated patients. Figure 1 shows the evolution of CD4 lymphocytes and plasma HIV RNA viral load during follow-up.

Discussion

The clinical presentation of primary HIV-1 infection varies from asymptomatic seroconversion to a severe symptomatic illness resembling infectious mononucleosis that can result in hospitalization (Schacker *et al,* 1996; Kassutto and Rosenberg, 2004; Huang *et al,* 2005). The most frequent neurological manifestation during primary HIV-1 infection is aseptic meningitis, although other disorders as cranial nerve VII palsy and radiculopathy have been described (Kassutto and Rosenberg, 2004). Although many patients seek medical attention during acute HIV-1 infection, the diagnosis is often missed (Rosenberg *et al,* 1999). Between 1997 and 2003, 75 patients with primary HIV infection were diagnosed in Hospital Clínic in Barcelona; 5 of these patients required hospital admission because of neurological symptoms and 3 (4%) had viral

Table 2 Blood and CSF laboratory findings

	Patients														
	1#	2#	3#	4*	5*	6*	7*	8*	9*	10*	11*	12*	13*	Median (IQR)
Blood														
CD4 lymphocytes (cells/mm^3)	315	200	570	551	591	264	434	585	391	319	487	709	190	434 (289.5–577.5)
HIV RNA load (copies/ml; log10)	7800	5100	140000	900000	4100000	—	$22x10^6$	1300000	$>10^6$	$>10^6$	151542	16600	259200	205371 ($14400–2 \times 10^6$)
	3.89	3.71	5.15	5.95	6.11		7.34	6.11	6.0	6.0	5.18	4.22	5.41	
CSF														
Glucose (mg/dl)	45	52	62	43	35	49	52	46	91	147	61	45	51	51 (45–61.5)
Proteins (mg/dl)	84	51	161	169	185	139	102	142	109	—	80	206	150	139 (82–165)
Leucocytes (cells/ml)	40	38	40	25	58	85	52	100	90	270	40	40	90	52 (40–90)
Lymphocytes (%)	89	95	27	—	72	95	71	95	50	99	—	92	—	90.5 (65.75–95)
ADA (IU/L)	9	10	6	11	16	—	4	10	5	—	—	5	4	7.5 (4.75–10.25)
HIV RNA load (copies/ml; log10)	2900	21000	—	100000	730000	—	560000	360000	—	250000	—	—	—	
	3.46	4.32		5	5.86		5.75	5.56		5.4				

#Meningoencephalitis after antiretroviral therapy interruption
*Meningoencephalitis during primary HIV-1 infection

Table 3 Antiretroviral regimen employed for each patient

Patient	Antiretroviral regimen	CNS Penetration-Effectiveness Score
1	zidovudine + lamivudine + efavirenz	2
2	zidovudine + lamivudine + lopinavir/ritonavir	2.5
3	zidovudine	1
4	no treatment	—
5	tenofovir + emtricitabine + lopinavir/ritonavir	2
6	zidovudine + lamivudine + lopinavir/ritonavir	2.5
7	zidovudine + lamivudine + lopinavir/ritonavir	2.5
8	tenofovir + emtricitabine + lopinavir/ritonavir	2
9	no treatment	—
10	stavudine + lamivudine + indinavir	2
11	tenofovir + didanosine + lopinavir/ritonavir	1
12	tenofovir + abacavir + lamivudine + lopinavir/ritonavir	2,5
13	stavudine + lamivudine + nelfinavir	1

meningitis (Sued *et al,* 2006). In a recent retrospective study of CSF samples, Hanson *et al*. reported that 3 of 57 (5%) patients with clinical signs and inflammatory findings on CSF study indicative of CNS infection had primary HIV infection, which had not been suspected or diagnosed (Hanson *et al,* 2007). To avoid delays in the diagnosis, these authors have suggested that assessment of patients with clinical and laboratory findings consistent with meningoencephalitis should include tests to detect acute HIV infection. In this report, we describe 10 patients with acute meningoencephalitis during primary HIV-1 infection and 3 patients who developed neurological impairment after interruption of antiretroviral therapy. This finding has been reported previously by Colven *et al*. in a series of three chronic HIV-1 infected patients presenting with retroviral rebound syndrome after cessation of suppressive antiretroviral therapy; one of these patients developed acute meningitis 3 weeks after the interruption (Colven *et al,* 2000).

The clinical presentation of patients with meningoencephalitis caused by HIV infection did not differ from that seen in other causes of meningoencephalitis. It is important to point out that most patients in our series presented with severe neurological manifestations, such as obtundation, focal neurological signs, agitation, and even seizures. The other neurological signs in our series consisted in uveomeningitis, ataxia, unilateral Bell palsy, dysarthria, and paresthesia. All these manifestations have been reported previously (Li *et al,* 2002; Pascual *et al,* 2005; Serrano *et al,* 2007). Moreover, 2 of our 13 cases presented generalized tonic-clonic seizures during the episode. In both cases, the electroence-

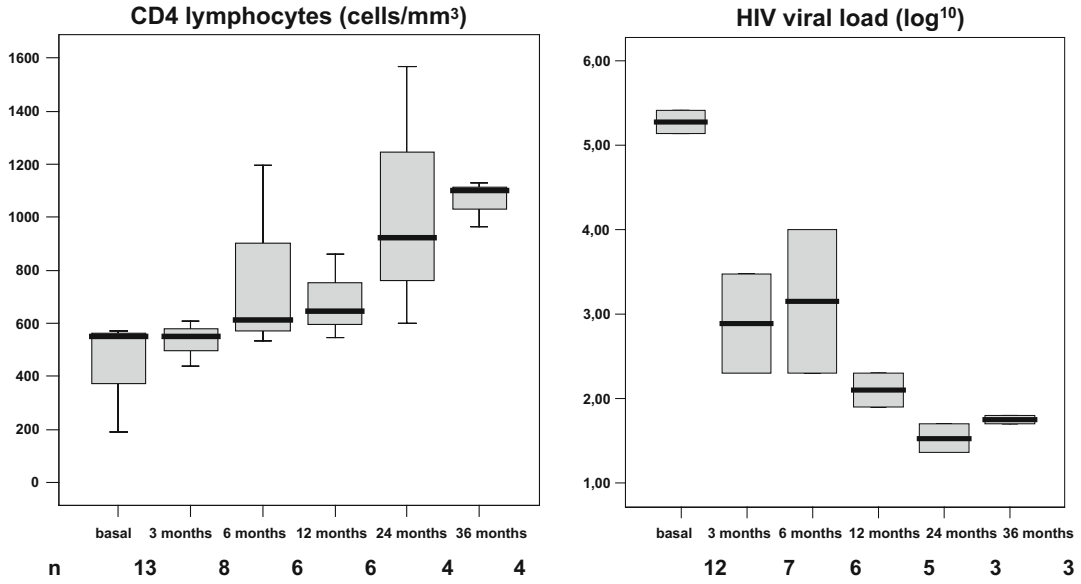

Figure 1 Evolution of CD4 lymphocytes (cells/mm^3) and plasma HIV-1 RNA viral load ($\log_{10}$ copies/ml) during follow-up.

phalogram demonstrated nonspecific global cortical dysfunction without paroxysms. Despite the presence of focal neurological signs, the radiological findings showed an absence of specific or focal abnormalities, except in one case, in which limbic encephalitis was detected in the cranial magnetic resonance study.

Two of the 10 patients in whom ADA levels were determined had an ADA value higher than 10 IU/L. In a previous report, this cut-off proved to be suggestive of tuberculous meningitis (Ribera *et al,* 1987). However, high ADA levels have been also described in patients with cytomegalovirus (CMV) neurological disease, and in cryptococcal, lymphomatous, and candidal meningitis (Corral *et al,* 2004). These findings show that acute HIV menigoencephalitis may be another cause of elevated ADA levels in CSF.

As has been reported, patients undergoing HIV-1 seroconversion with acute neurological symptoms had significantly higher mean CSF HIV-1 viral load than did patients without neurological syndromes (Tambussi *et al,* 2000; Mellgren *et al,* 2005; Wendel and McArthur, 2003). Tambussi *et al* compared HIV-1 viral load in CSF between patients with and without neurological syndrome; a strong correlation between neurological symptoms and viral load was found. Mean CSF HIV level was significantly higher in patients with neurological symptoms (4.12 log) than in those without (2.58 log) (Tambussi *et al,* 2000). In patients with acute meningitis after antiretroviral treatment interruption, HIV-1 viral load was considerably higher in CSF than in plasma (Colven *et al,* 2000).

Despite the presence of severe neurological manifestations, in the vast majority of cases reported in the literature, as well as in ours, the clinical outcome is favorable, with complete recovery and no after-effects.

Early diagnosis of acute HIV-1 infection often creates a dilemma for clinicians with regard to treatment. Potential benefits of early antiretroviral therapy have been suggested, but differences in morbidity and mortality have not been proven. The theoretical benefits that are frequently discussed must be weighed against the significant risk of long-term medication toxicity and cost (Kassutto and Rosenberg, 2004).

The rational basis to initiate antiretroviral treatment in patients with acute neurological manifestations during primary HIV infection derives from cohort studies. In a cohort of 277 adults enrolled more than 1 year after HIV-1 primary infection, Boufassa *et al* demonstrated that the relative risk of developing AIDS was 6.11 in patients with neurological manifestations during primary infection and 2.32 in those with non-neurological manifestations, as compared to a group of patients showing no clinical manifestations during primary infection (Boufassa *et al,* 19957). Apart from a reduced chance of developing acquired immunodeficiency syndrome (AIDS)-defining diseases, early antiretroviral therapy may result in more rapid resolution of symptoms, particularly in cases with severe neurological manifestations.

Eleven patients in our series initiated antiretroviral treatment following the neurological presentation. We cannot affirm that their clinical improvement was due to the treatment, because spontaneous resolution has also been described. However, as in other viral illnesses, resolution of the neurological symptoms may have been accelerated by antiretroviral therapy, which is particularly important in patients with severe manifestations

such as seizures. The two patients who did not receive antiretroviral treatment presented spontaneous improvement; hence, therapy was deferred. Letendre *et al* demonstrated that a lower cerebral penetration-effectiveness score of antiretroviral regimen correlated with higher CSF viral loads (Letendre *et al,* 2008). Ranks less than 2 were associated with an 88% increase in the odds of detectable CSF viral load. Poorer penetration of antiretroviral (ARV) drugs into the CNS appears to allow continued HIV replication in the CNS, as indicated by higher CSF HIV viral loads. In our study, 8 of the 11 treated patients had a CPE ≥ 2, although we could not assess the evolution of HIV viral load in CSF. Because inhibition of HIV replication in the CNS is probably critical in treating patients who have HIV associated neurocognitive disorders, antiretroviral treatment strategies that account for CNS penetration should be considered in patients with neurological manifestations during primary infection. Recently Gasnault *et al* have observed in patients with progressive multifocal leukoencephalopathy that the use of an antiretroviral regimen, including drugs with high penetration into the CNS, lead to a better survival (Gasnault *et al,* 2008).

In conclusion, neurological impairment during primary HIV-1 infection or after interrupting antiretroviral therapy is a relatively uncommon manifestation that tends to recover spontaneously. Although initiation of antiretroviral therapy in these patients is still not well established, emerging data suggest its potential benefit.

Patients and methods

From 1999 to January 2007, we retrospectively identified and reviewed 13 patients with a clinical diagnosis of meningitis or meningoencephalitis during acute HIV-1 infection ($n=10$) or after withdrawal of antiretroviral therapy ($n=3$). The study was performed in two hospitals in Barcelona (Hospital Universitari Vall d'Hebron and Hospital Clínic i Provincial).

To be included in the study, patients had to meet the following criteria: (1) diagnosis of meningitis or meningoencephalitis defined by the presence of fever and/or headache, cerebrospinal fluid (CSF) leukocyte count >10 cells/mm^3, and CSF protein count >50 mg/dl. When confusion, seizures, or any other focal neurological signs were present, a diagnosis of meningoencephalitis was established; (2) exclusion of other potential causes of meningitis or meningoencephalitis; (3) diagnosis of acute HIV-1 infection defined by all the following criteria: negative or indeterminate Western blot tests, detectable plasma HIV RNA, and complete seroconversion after the episode. Meningoencephalitis after antiretroviral therapy withdrawal was established when the above-mentioned criteria manifested during a period of 1 to 10 weeks after stopping antiretroviral treatment.

The following data were recorded for all patients: gender, age, race, risk factors for acquiring HIV infection, clinical manifestations, neurological complications, and outcome. In patients with meningoencephalitis after antiretroviral therapy withdrawal, the years of HIV infection and days without antiretroviral therapy were reviewed. Antiretroviral therapy was recorded for each patient. Each antiretroviral was given a Cerebral Penetration-Effectiveness (CPE) rank of 0 (low: ddI, TNF, ddC, APV, NFV, RTV, SQV, SQV/r, TPV/r, T20), 0.5 (intermediate: 3TC, d4T, EFV, APV/r, FPV/r, ATZ/r, DRV/r), or 1 (high: ABC, FTC, AZT, DLV, NVP, IDV, IDV/r, LPV/r) based on their chemical properties, concentrations in CSF, and/or effectiveness in the central nervous system (CNS) in clinical studies (Letendre *et al,* 2008; Gasnault *et al,* 2008). Laboratory parameters included total leukocyte count, platelet count, CD4 lymphocyte count (cells/mm^3), plasma HIV RNA load (copies/ml), and the following CSF parameters: cell count, glucose (mg/dl), proteins (mg/dl), and CSF HIV-1 viral load (copies/ml). Microbiological determinations performed to exclude other diagnoses included Gram, Ziehl-Nielssen, and India-ink stains, bacterial, mycobacterial, and fungal cultures, latex cryptococcal antigen, herpes virus family polymerase chain reaction (PCR), and adenosine deaminase (ADA) (IU/L). In our laboratory, ADA levels >10 IU/L are considered to be highly suggestive of tuberculosis (Ribera *et al,* 1987).

Cranial magnetic resonance imaging and/or computerized tomography as well as electroencephalography (EEG) were performed at the discretion of the attending physician.

Quantitative variables are expressed as medians and interquartile range (IQR) and qualitative variables as frequencies and percentages.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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This paper was first published online on iFirst on 24 November 2008.